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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,403	04/15/2002	Donald Gullberg	10142.0001	3147

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,403	GULLBERG, DONALD	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 156-162* is/are pending in the application.

4a) Of the above claim(s) *26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *156-162* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/07 has been entered.

2. Claims 26 and 156-162 are pending.

3. Claim 26 is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 156-162 are under consideration in the instant application as they read on a recombinant or isolated integrin subunit α11 having the amino acid sequence encoded by SEQ ID NO: 1.

5. Applicant's IDS, filed 4/30/07, is acknowledged.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 161-162 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "a heterodimer comprising: (a) the extracellular domain of integrin subunit α11 according to claim 156; and (b) the integrin subunit β1" claimed in claim 161 and the phrase "the heterodimer of claim 161, wherein the extracellular domain of integrin of integrin subunit α11 is non-covalently associated with the integrin subunit β1" represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 9/7/06 does not point to the specification for support for the newly added limitations as claimed in claims 161-162. However, the specification does not provide a clear support for such limitation. The extracellular domain of α11 heterodimer with β1 limitations was not contemplated in the specification and claims as originally filed. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 156-162 rejected under 35 U.S.C. 103(a) as being unpatentable over Gullberg *et al* (Dev. Dyn. 204:57-65, 1995) (IDS Ref. No. C2), as is evidenced by Velling *et al* (IDS Ref. No. C5), in view of in view of Alberts *et al* (1989) and US. 6,046,316 patent.

Gullberg *et al* teach an isolated integrin subunit αmt obtained from G6 myoblasts and myotubes. Gullberg *et al* teach that αmt is induced upon myogenic differentiation (see abstract). Gullberg *et al* teaches that under non-reducing conditions β1 associated protein migrated as 145 kD, wherein under reducing conditions, β1 integrin associated protein migrated in SDS-PAGE as a 155 kD protein (see abstract in particular). Gullberg *et al* teach that αmtβ1 heterodimer (see page 60, 2nd col., 2nd ¶ in particular).

The claimed invention differs from the reference teachings only by the recitation of the extracellular domain of integrin subunit α11 comprising amino acids 23-1141 of SEQ ID NO: 2 in claim 156, a fragment of the extracellular domain of integrin subunit α11 comprises the I-domain of integrin subunit α11 from amino acids 159 to 355 of SEQ ID NO: 2 in claim 157, or comprises amino acids 804 to 826 of SEQ ID NO: 2 in claim 158. The cytoplasmic domain of integrin subunit α11 comprising amino acids 1165 to 1188 of SEQ ID NO: 2 in claim 159 or the transmembrane domain of integrin subunit α11 comprising amino acids 1142 to 1164 of SEQ ID NO:2 in claim 160 and the heterodimer recited in claims 161 and 162.

Alberts *et al* teach once a protein has been purified to homogeneity, its biological activities can be examined in detail. A small part of the protein's amino acid sequence can be determined and its gene can be cloned; the remaining amino acid sequence is then obtained from the nucleotide sequence of the gene (page 174, under Summary in particular). Further, Alberts *et al* teach genetic engineering techniques using selecting regions of a known amino acid sequence to make synthetic oligonucleotide probes to identify the clones of interest in a DNA library (see page 262, 3rd paragraph and Fig. 5-84 in particular). Further, Alberts *et al* teach the recombinant DNA technology has revolutionized the study of the cell. Any region of a cell's DNA can now be excised with restriction nucleoases and inserted into a self-replicating genetic element (a plasmid) to produce a "genomic DNA clone". Unlimited amounts of a highly purified DNA

molecule can thereby be obtained and its nucleotide sequence determined at a rate of hundreds of nucleotides per day, revealing the amino acid sequence of the protein it encodes (see page 196 under Summary in particular). Alberts et al (page 821-823, Figure 14-52) further teach that integrins is a noncovalently associated complex of two distinct chains called α and β. The α chain is usually made of one small transmembrane chain (comprising transmembrane domain and cytoplasmic domain) and one large extracellular chain (see Fig. 14-52 in particular). Figure 14-52, on page 821, depicts diagrammatic representation of the structure of the generic integrin α and β subunits. Finally, Alberts et al teach that the fibronectin integrin functions as a transmembrane linker to mediate interactions between the actin cytoskeleton inside the cell and fibronectin in the extracellular matrix (see page 821, last ¶ in particular).

The US. `316 patent teaches that integrins generally contain a large extracellular domain formed by the α (~1,000 amino acids) and β (~750 amino acids) subunit, a single transmembrane segment from each subunit, and two short cytoplasmic tails, with the exception of β4, whose cytoplasmic tail is more than 1,000 amino acid residues in length. The α subunit is a single gene product that is postranslationally cleaved into the light and heavy chain which are re-connected by a disulfide bond. The light chain of the α subunit contains the transmembrane and the cytoplasmic tail. Even though integrins were originally thought to function purely as anchor molecules, they are also known as signaling receptors. Integrin cytoplasmic tails do not have intrinsic enzymatic activity, but by recruiting and activating tyrosine (pp125FAK, pp60src), serine (PKCa, ERK, JNK, ILK) or lipid (cPLA2, PI3K, PI4P5K) kinases, they can simultaneously control multiple signaling pathways such as the MAP kinase and JAK-TAT pathways (see col., 1 lines 35-60 in particular). Also, the `316 patent teaches that integrins can be activated by extracellular signals such as divalent cations ($Mn^{2+}$, $Ca^{2+}$) or by treatment with certain activating mAbs (see col., 2 lines 19-21 in particular). The `316 patent further teach that several reports in the literature indicate that inside-out signaling is mediated by the cytoplasmic tail of the α subunit, and outside-in signaling by the cytoplasmic tail of the β subunit (see col., 2 lines 30-33 in particular). Figure 1D, depicts schematic representation of the predicted structure of the generic integrin α subunit comprising extracellular domain, transmembrane domain and cytoplasmic tail. Fig. 6B depicts a schematic representation of the structure of an integrin with wild type β3 and truncated αIIb subunits (lacks both transmembrane and cytoplasmic domains) (heterodimer). Finally, the `316 patent teaches that transfection with mutant αIIb constructs that either have a point mutation in the cytoplasmic tail or complete deletion of the tail, result in constitutive expression of the integrin in a high affinity state (see col., 3, lines 15-17 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the amino acid sequence αmt subunit taught by Gullberg *et al* using the genetic engineering techniques as taught by Albert *et al*. Integrins have conserved structural and functional features, the structure and ultimate function of a given protein chain are often best achieved at the domain level. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify the αmt domains within a protein sequence such

as the extracellular, the cytoplasmic and the transmembrane domains as taught by Alberts et al and the `316 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the extracellular domain which can be activated by extracellular signals such as divalent cations (Mn^{2+}, Ca^{2+}) or by treatment with certain activating mAbs involve in ligand/integrin interaction function and the skilled in the art would be motivated to do so to determine the extracellular domain binding components of the extracellular matrix (ECM). Further, because the cytoplasmice tail of the α subunit involve in inside-out signaling is mediated by the cytoplasmic tail of the α subunit. Also, the ordinary skilled in the art would be motivated to study the structure/function relationship of each domain rather than αmt as whole chain in order to gain an insight into the structure and ultimate function of αmt structural domains. One of ordinary skill in the art at the time the invention was made would have been motivated to construct a heterodimer of the extracellular domain of αmt with β1 chain to obtain a high affinity state expression of the integrin.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

July 10, 2007

Maher Haddad

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